

**III. Remarks**

**A. Amendments to the Claims**

Applicants have amended claims 8–9, 13–16 and 20–25 to further define the suspension. The suspension is now defined as comprising primary particles which are stabilized against agglomeration by precipitation reactions from acidic aqueous solutions of water-soluble calcium salts and water-soluble phosphate or fluoride salts in the presence of a defined colloid at an increased pH using an aqueous alkali or ammonia. Support for the amendment is provided in the Specification at page 7, line 19, to page 8, line 4.

**B. Rejections Under 35 U.S.C. Section 103 — Obviousness**

Claims 8, 9, 13–16 and 20–25 are rejected under 35 U.S.C. Section 103(a) as being unpatentable over United States Patent No. 6,919,070 to Rudin et al., in view of United States Patent No. 5,560,932 to Bagchi et al.

**1. The Examiner's reasons for the rejection**

The Examiner's reasons for the rejection are as follows:

Rudin et al. has been discussed [at] length in previous office actions. Humectants are included in the compositions and comprise 0 to 80% of the compositions (col. 3, lines 19–25). The reference differs from the instant claims insofar as it does not disclose surface treatment of the inorganic particles (hydroxyapatite and other abrasives) contained in its dentifrice compositions.

Bagchi et al. disclose[s] pharmaceutical particles having an extremely small effective average particle size [that] can be prepared by homogeneous nucleation and precipitation in the presence of a surface modifier and that such particles are stable and do not appreciably flocculate or aggregate due to interparticle attractive force (col. 4, lines 41-50). Surface modifying agents include gelatin, casein, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose and hydroxypropylcellulose (col. 5, lines 44-56). The particles have a particle size of less than 400 nm to less than 100 nm (col. 6, lines 28-50). The reference differs from the instant claims insofar [as] it does not disclose the particles are hydroxyapatite [and] the compositions are oral care compositions.

Although the secondary reference does not specifically disclose dental abrasives, it is still applicable to the instant case because it gives a general teaching of how small particles aggregate due to interparticle attractive forces. This appears to be based on the physical characteristic of the particle and not its chemical makeup. Therefore it would apply not only to pharmaceuticals but also to dental abrasives.

That being said, it would have been obvious to one of ordinary skill in the art to have used surface modifiers to coat the hydroxyapatite of the primary reference motivated by the desire to stabilize the particles and to inhibit aggregation due to interparticle attractive force as disclosed by the secondary reference.

(Examiner's Action, page 3, line 3, to page 4, line 7).

## **2. Legal standard for determining whether Applicants' claims are obvious under 35 U.S.C. Section 103**

The legal interpretation of Section 103 to be applied is set forth in the recent Supreme Court decision of *KSR International Co. v. Teleflex Inc.* (KSR), 550 U.S. \_\_\_, 82 USPQ2d 1385 (2007). KSR cites *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 148 USPQ 459 (1966) as setting out an objective analysis for applying Section 103. (82 USPQ2d at 1388). The objective analysis is as follows:

Under § 103, the scope and content of the prior art are to be determined; the differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

(148 USPQ at 467).

Accordingly, the factual inquiries set forth by the Court are as follows:

- [T]he scope and content of the prior art are . . . determined;
- Differences between the prior art and the claims at issue are . . . ascertained;
- The level of ordinary skill in the prior art [is] resolved; and
- Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized. . . .

**3. The Application of the *Graham v. John Deere Co.* factual standards**

The application of the *Graham v. John Deere Co.* factual standards is being made with Declarations of Dr. Christian Kropf, one of the inventors of the invention disclosed and claimed in this application. (The Third Declaration of Dr. Christian Kropf was originally filed with Applicants' Amendment and Response dated February 4, 2008 (attached as **EXHIBIT B**). For the filing of Applicants' present Amendment and Response, the Third Declaration of Dr. Christian Kropf is attached and designated **EXHIBIT A**. A Fourth Declaration of Dr. Christian Kropf is attached and designated **EXHIBIT B**.

**(a) Determining the scope and content of the prior art**

The Rudin et al. patent discloses a composition characterized in that it comprises particles of hydroxyapatite with an average particle size in length (l), width (d), and thickness (h). The values for these dimensions are: (l) from 0.2  $\mu\text{m}$  to 0.01  $\mu\text{m}$ , (d) 0.1  $\mu\text{m}$  to about 0.001  $\mu\text{m}$  and (h) from 0.1  $\mu\text{m}$  to 0.0001  $\mu\text{m}$  (column 2, lines 22–27) (Third Declaration of Christian Kropf, Paragraph 5).

Rudin et al. further discloses that the hydroxyapatite being introduced into the composition possesses osteo-reparative properties and contains preferably about 100%  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$  and that the specific surface of hydroxyapatite used in the composite advantageously is 100 to 150  $\text{m}^2/\text{g}$  (column 2, lines 41–45). This disclosure indicates that the hydroxyapatite disclosed in Rudin et al. is pure hydroxyapatite (Third Declaration of Christian Kropf, Paragraph 6).

Rudin et al. further discloses an oral product that will comprise a liquid phase containing humectants and binding thickeners which act to maintain the particulate solid abrasive and hydroxyapatite crystals in the form of stable suspension in liquid phase (column 3, lines 11–15). On the basis of the disclosure in Rudin et al., the hydroxyapatite crystals in the suspension are pure hydroxyapatite (Third Declaration of Christian Kropf, Paragraphs 6 and 7).

The conclusion that the hydroxyapatite particles disclosed in Rudin et al. are pure is further based on the disclosure at column 2, lines 46–51 of Rudin et al. that U.S. Patent No. 6,254,855 B1 describes a method for producing a suspension of hydroxyapatite as described in the Rudin et al. application. U.S. Patent No. 6,254,855 B1 discloses in EXAMPLE 1 that according to the method described in that patent, a pure stoichiometric hydroxylapatite in a suspension form is produced free of admixtures (column 3, lines 43–67) (Third Declaration of Christian Kropf, Paragraph 8).

The Bagchi et al. patent describes the preparation of a nanoparticulate dispersion and the resulting nanoparticles. The process is summarized in the Abstract, the pertinent portion of which is set forth below.

This invention describes the preparation of nanoparticulate pharmaceutical agent dispersion via a process that comprises the dissolution of the said pharmaceutical agent in an alkaline solution and then neutralizing the said solution with an acid in the presence of a suitable surface-modifying, surface-active agent to form a fine particle dispersion of the said pharmaceutical agent.

(Fourth Declaration of Christian Kropf, Paragraph 5).

Bagchi et al. discloses the objective of the invention at column 3, lines 7-16, which is quoted herebelow:

It would be desirable to provide stable dispersible drug or pharmaceutical agent particles in submicron size range which can be readily prepared which do not appreciably flocculate or agglomerate due to interparticle attraction forces, and do not require the presence of a crosslinked matrix, simultaneously providing enhanced bioavailability of the drug. Furthermore, it would be highly desirable that such formulations do not involve removal of toxic residues such as toxic solvents or heavy metal solubilizates that arise out of attrition of the milling media.

(Fourth Declaration of Christian Kropf, Paragraph 6).

The accomplishment of this objective by the Bagchi et al. invention is referred to in the following description of the advantages of the invention.

It is an advantageous feature that a wide variety of surface modified drug nanoparticles free of unacceptable contamination can be prepared in accordance with this invention. (Column 3, lines 50-52).

A further advantage of the method is that unlike solvent precipitation, the final product of this invention is free of any trace of trace solvents that may be toxic and must be removed by expensive treatments prior to final product formulation. (Column 4, lines 7-11).

(Fourth Declaration of Christian Kropf, Paragraph 7).

The particles of the invention, the process of making the particles and a preferred utility are disclosed in the paragraph directly under the heading "Description of Preferred Embodiments." That paragraph is set forth below.

This invention is based partly on the discovery that pharmaceutical agent particles having an extremely small effective average particle size can be prepared by homogeneous nucleation and precipitation in the presence of a surface modifier, and that such particles are stable and do not appreciably flocculate or aggregate due to interparticle attractive force and can be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability. (Column 4, lines 40-48).

(Fourth Declaration of Christian Kropf, Paragraph 8).

Bagchi et al. discloses that the particles comprise a pharmaceutical agent substance in a discrete crystalline phase. (Column 4, lines 56-61) (Fourth Declaration of Christian Kropf, Paragraph 9).

Bagchi et al. discloses that the surface modifier adheres to the surface of the particles but is free of intermolecular linkages between the molecules of the modifier, and between the modifier and the particles, due to the lack of chemical bonds between the surface modifier and [drug] particle. This disclosure in Bagchi et al. is set forth at column 5, lines 43–46 and in the passage herebelow:

The surface modifier is adsorbed on the surface of the pharmaceutical agent in an amount sufficient to maintain an effective average particle size of less than about 400 nm. The surface modifier does not chemically react with the drug substance or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages. (Column 6, lines 20–26).

(Fourth Declaration of Christian Kropf, Paragraph 10).

**(b)     Ascertaining the differences  
          between the prior art and the claims at issue**

Claim 8 of the application is directed to a suspension. The remaining claims 9, 13–16 and 20–25 are directed to a toothpaste comprising the suspension, or other suspensions within the scope of claim 8. Claim 8 reads as follows:

Claim 8.         A suspension of one or more phosphate calcium salts, fluoride calcium salts, or fluorophosphate calcium salts in a liquid medium in which the salts are less than 1 g/l soluble, wherein the calcium salts comprise primary particles having diameters of from 5 to 50 nanometers and lengths of from 10 to 150 nanometers, wherein the calcium salts are formed by precipitation reactions from acidic aqueous solutions of water-soluble calcium salts and aqueous solutions of water-soluble phosphate or fluoride salts at an increased pH using an aqueous alkali or ammonia and in the presence of a content of at least 0.01% by weight, based on the weight of the suspension, of a water-soluble polymeric protective colloid selected from the group consisting of gelatin, casein, starch, plant gums, cellulose ethers, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, hydroxyethylstarch and hydroxypropylguar, resulting in the colloid being adsorbed onto said particles and the particles being stabilized against agglomeration.

(Fourth Declaration of Christian Kropf, Paragraph 4).

A comparison of the suspension claimed in Claim 8 with the suspension disclosed in Rudin et al. reveals that the claimed suspension is distinct from the suspension taught or suggested by Rudin et al. Rudin et al. discloses crystals of pure hydroxyapatite of a defined particle size that are maintained in a suspension. Applicants' claimed suspension is of particles of calcium salts, wherein a defined water-soluble polymeric protective colloid, in particular, gelatin, is adsorbed onto said particles. Accordingly, Rudin et al. does not disclose or suggest Applicants' claimed suspension comprising particles of one or more calcium salts with a colloid (gelatin) adsorbed onto said particles, which is set forth in all of Applicants' pending claims 8-9, 13-16 and 20-25 (Third Declaration of Christian Kropf, Paragraph 10).

Applicants' process of making the particles is different from the process used to make the Bagchi et al. particles. Applicants' process as disclosed in the Specification at page 7, lines 13-19, prepares the claimed suspensions by precipitation reactions from acidic aqueous solutions of water-soluble calcium salts and aqueous solutions of water-soluble phosphate or fluoride salts in the presence of water-soluble polymeric protective colloids. Applicants' precipitation reactions are carried out at an increased pH using an aqueous alkali or ammonia. The Bagchi et al. process begins with the dissolution of a pharmaceutical agent in an aqueous base and the addition of an aqueous surfactant solution followed by the addition of an acid solution to form a nanoparticulate dispersion. (See Steps 1-3 on the cover sheet of the Bagchi et al. patent). As noted above in Paragraph 8, the Bagchi et al. particles can be prepared by homogeneous nucleation and precipitation in the presence of a surface modifier. (Fourth Declaration of Kropf, Paragraph 11).



Unlike the Bagchi et al. process in which the particles are formed by homogeneous nucleation, the calcium salt particles of Applicants' claimed suspension are formed from precipitation reactions of acidic aqueous solutions of water-soluble calcium salts and of aqueous solutions of water-soluble phosphate or fluoride salts. Applicants' precipitation reactions occur under conditions of increasing pH using an aqueous alkali or ammonia in the presence of one or more of Applicants' claimed colloids rather than under conditions of decreasing pH as disclosed in Bagchi et al. Applicants' precipitation reactions of acidic aqueous solutions of water-soluble calcium and phosphate or fluoride salts, in the presence of the colloid, and at an increasing pH, results in particles having a more intense structure in which, in Applicants' claimed particles, the colloid forms intermolecular crosslinkages. In contrast, in the Bagchi et al. particles, the surface modifiers [*i.e.*, colloid] are essentially free of intermolecular crosslinkages. (Fourth Declaration of Kropf, Paragraph 12).

Accordingly, the disclosure of Bagchi et al. relied upon by the Examiner, *i.e.*, the absence of intermolecular, *i.e.*, interparticle attractive, forces and chemical bonding between the surface modifiers and the surface modifiers and particles to avoid the aggregation of small particles. The Bagchi et al. disclosure teaches away from Applicants' claimed particles, which are chemically bonded to the colloid and possess intermolecular crosslinkages.

Hence, the Bagchi disclosure has very little relevance to Applicants' claimed suspension.

**(c) Resolving level of ordinary skill in pertinent art**

The inventors of the present application, one of whom is Dr. Christian Kropf, and the inventors of the Rudin et al. and Bagchi et al. patents, would represent persons of ordinary skill in the art.

(d) **Possible utilization of secondary considerations**

As set forth in *Graham v. John Deere Co.*:

Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

(148 USPQ at 467).

As set forth above, Rudin et al. and Bagchi et al. have failed to discover, let alone exemplify, disclose or suggest to one of ordinary skill in the art, Applicants' claimed suspension.

**4. Applicants' claims are patentable over Bagchi et al.**

As noted above, Applicants disclose and claim a suspension of particles which are modified and stabilized against coagulation and agglomeration by a water-soluble protective colloid adsorbed onto the particles. Applicants' modified and stabilized particles constitute particles having intermolecular crosslinkages. Bagchi et al. discloses that its particles and surface modifier are essentially free of intermolecular crosslinkage.

Accordingly, one of ordinary skill in the art could not derive Applicants' claimed suspension of particles from Bagchi et al. Therefore, Rudin et al. and Bagchi et al. fail to recognize, let alone exemplify, disclose or even suggest to one of ordinary skill in the art the suspension set forth in all of Applicants' claims 8-9, 13-16 and 20-25. Bagchi et al. illustrates the failure of others to recognize, let alone suggest, Applicants' claimed invention.

Accordingly, for the reasons set forth above, the rejection of claims 8-9, 13-16 and 20-25 under 35 U.S.C. Section 103(a) as being unpatentable over United States Patent No. 6,919,070 to Rudin et al. in view of United States Patent No. 5,560,932 to Bagchi et al. is untenable and should be withdrawn.

**IV. Conclusion**

It is believed that the above Amendment and Remarks constitute a complete response under 37 C.F.R. Section 1.111 and that all bases of rejection in the Examiner's Action have been adequately rebutted or overcome. A Notice of Allowance in the next Office Action is, therefore, respectfully requested. The Examiner is requested to telephone the undersigned attorney if any matter that can be expected to be resolved in a telephone interview is believed to impede the allowance of pending claims 8-9, 13-16 and 20-25 of United States Patent Application Serial No. 09/868,379.

Respectfully submitted,

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